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(54) Title: AN ASYMMETRIC CONJUGATE ADDITION REACTION

(57) Abstract

This invention relates to a key intermediate in the synthesis of an endothelin antagonist and the synthesis of this key intermediate using an asymmetric conjugate addition reaction.

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TITLE OF THE INVENTION

AN ASYMMETRIC CONJUGATE ADDITION REACTION

BACKGROUND OF THE INVENTION

The present invention relates to novel key intermediates in the synthesis of an endothelin antagonist and the method for preparing these key intermediates of formula I.

Two endothelin receptor subtypes ET_A and ET_B are known so far. The compounds of the present invention possess high affinity to at least one of two receptor subtypes, responsible for the dilation of smooth muscle, such as blood vessels or in the trachea. The endothelin antagonist compounds of the present invention provide a new therapeutic potential, particularly for the treatment of hypertension, pulmonary hypertension, Raynaud's disease, acute renal failure, myocardial infarction, angina pectoris, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, gastric ulcer, diabetes, restenosis, prostatauxe endotoxin shock, endotoxin-induced multiple organ failure or disseminated intravascular coagulation, and/or cyclosporin-induced renal failure or hypertension.

Endothelin is a polypeptide composed of amino acids, and it is produced by vascular endothelial cells of human or pig. Endothelin has a potent vasoconstrictor effect and a sustained and potent pressor action (Nature, 332, 411-415 (1988)).

Three endothelin isopeptides (endothelin-1, endothelin-2 and endothelin-3), which resemble one another in structure, exist in the bodies of animals including human, and these peptides have vasoconstriction and pressor effects (Proc. Natl. Acad, Sci, USA, 86, 2863-2867 (1989)).

As reported, the endothelin levels are clearly elevated in the blood of patients with essential hypertension, acute myocardial infarction, pulmonary hypertension, Raynaud's disease, diabetes or atherosclerosis, or in the washing fluids of the respiratory tract or the blood of patients with asthmaticus as compared with normal levels (Japan, J. Hypertension, 12, 79, (1989), J. Vascular medicine Biology,

2, 207 (1990), Diabetologia, 33, 306-310 (1990), J. Am. Med. Association, 264, 2868 (1990), and The Lancet, ii, 747-748 (1989) and ii, 1144-1147 (1990)).

Further, an increased sensitivity of the cerebral blood vessel to endothelin in an experimental model of cerebral vasospasm (Japan. Soc. Cereb. Blood Flow & Metabol., 1, 73 (1989)), an improved renal function by the endothelin antibody in an acute renal failure model (J. Clin, invest., 83, 1762-1767 (1989), and inhibition of gastric ulcer development with an endothelin antibody in a gastric ulcer model (Extract of Japanese Society of Experimental Gastric Ulcer, 50 (1991)) have been reported. Therefore, endothelin is assumed to be one of the mediators causing acute renal failure or cerebral vasospasm following subarachnoid hemorrhage.

Further, endothelin is secreted not only by endothelial cells but also by tracheal epithelial cells or by kidney cells (FEBS Letters, 255, 129-132 (1989), and FEBS Letters, 249, 42-46 (1989)).

Endothelin was also found to control the release of physiologically active endogenous substances such as renin, atrial natriuretic peptide, endothelium-derived relaxing factor (EDRF), thromboxane A2, prostacyclin, noradrenaline, angiotensin II and substance P (Biochem. Biophys, Res. Commun., 157, 1164-1168 (1988); Biochem. Biophys, Res. Commun., 155, 20 167-172 (1989); Proc. Natl. Acad. Sci. USA, 85 1 9797-9800 (1989); J. Cardiovasc. Pharmacol., 13, S89-S92 (1989); Japan. J. Hypertension, 12, 76 (1989) and Neuroscience Letters, 102, 179-184 (1989)). Further, endothelin causes contraction of the smooth muscle of gastrointestinal tract and the uterine smooth muscle (FEBS Letters, 247, 337-340 (1989); Eur. J. Pharmacol., 154, 227-228 (1988); and Biochem. Biophys Res. Commun., 159, 317-323 (1989)). Further, endothelin was found to promote proliferation of rat vascular smooth muscle cells, suggesting a possible relevance to the arterial hypertrophy (Atherosclerosis, 78, 225-228 (1989)). Furthermore, since the endothelin receptors are present in a high density not only in the peripheral tissues but also in the central nervous system, and the cerebral administration of endothelin induces a

behavioral change in animals, endothelin is likely to play an important role for controlling nervous functions (Neuroscience Letters, 97, 276-279 (1989)). Particularly, endothelin is suggested to be one of mediators for pain (Life Sciences, 49, PL61-PL65 (1991)).

Internal hyperplastic response was induced by rat carotid artery balloon endothelial denudation. Endothelin causes a significant worsening of the internal hyperplasia (J. Cardiovasc. Pharmacol., 22, 355 - 359 & 371 - 373(1993)). These data support a role of endothelin in the phathogenesis of vascular restenosis. Recently, it has been reported that both ET_A and ET_B receptors exist in the human prostate and endothelin produces a potent contraction of it. These results suggest the possibility that endothelin is involved in the pathophysiology of benign prostatic hyperplasia (J. Urology, 151, 763 - 766(1994), Molecular Pharmocol., 45, 306 - 311(1994)).

On the other hand, endotoxin is one of potential candidates to promote the release of endothelin. Remarkable elevation of the endothelin levels in the blood or in the culture supernatant of endothelial cells was observed when endotoxin was exogenously administered to animals or added to the culture endothelial cells, respectively. These findings suggest that endothelin is an important mediator for endotoxin-induced diseases (Biochem. Biophys. Commun., 161, 1220-1227 (1989); and Acta Physiol. Scand., 137, 317-318 (1989)).

Further, it was reported that cyclosporin remarkably increased endothelin secretion in the renal cell culture (LLC-PKL cells) (Eur. J. Pharmacol., 180, 191-192 (1990)). Further, dosing of cyclosporin to rats reduced the glomerular filtration rate and increased the blood pressure in association with a remarkable increase in the circulating endothelin level. This cyclosporin-inducea renal failure can be suppressed by the administration of endothelin antibody (Kidney Int., 37, 1487-1491 (1990)). Thus, it is assumed that endothelin is significantly involved in the pathogenesis of the cyclosporin-induced diseases.

Such various effects of endothelin are caused by the binding of endothelin to endothelin receptors widely distributed in many tissues (Am. J. Physiol., 256, R856-R866 (1989)).

It is known that vasoconstriction by the endothelins is caused via at least two subtypes of endothelin receptors (J. Cardiovasc. Pharmacol., 17(Suppl.7), S119-SI21 (1991)). One of the endothelin receptors is ET_A receptor Selective to ET-1 rather than ET-3, and the other is ET_B receptor equally active to ET-1 and ET-3. These receptor proteins are reported to be different from each other (Nature, 348, 730-735 (1990)).

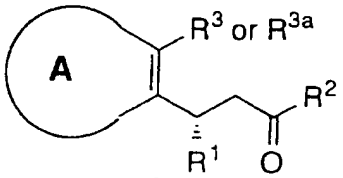
These two subtypes of endothelin receptors are differently distributed in tissues. It is known that the ET_A receptor is present mainly in cardiovascular tissues, whereas the ET_B receptor is widely distributed in various tissues such as brain, kidney, lung, heart and vascular tissues.

Substances which specifically inhibit the binding of endothelin to the endothelin receptors are believed to antagonize various pharmacological activities of endothelin and to be useful as a drug in a wide field. Since the action of the endothelins is caused via not only the ET_A receptor but also the ET_B receptor, novel non-peptidic substances with ET receptor antagonistic activity to either receptor subtype are desired to block activities of the endothelins effectively in various diseases.

Endothelin is an endogenous substance which directly or indirectly (by controlling liberation of various endogenous substances) induces sustained contraction or relaxation of vascular or non-vascular smooth muscles, and its excess production or excess secretion is believed to be one of pathogeneses for hypertension, pulmonary hypertension, Raynaud's disease, bronchial asthma, gastric ulcer, diabetes, arteriosclerosis, restenosis, acute renal failure, myocardial infarction, angina pectoris, cerebral vasospasm and cerebral infarction. Further, it is suggested that endothelin serves as an important mediator involved in diseases such as restenosis, prostatauxe, endotoxin shock, endotoxin-induced multiple organ failure or disseminated intravascular

coagulation, and cyclosporin-induced renal failure or hypertension. Two endothelin receptors ET_A and ET_B are known so far. An antagonistic agent against the ET_B receptor as well as the ET_A receptor is useful as a drug. In the field of anti-endothelin agents, some non-peptidic compounds possessing antagonistic activity against endothelin receptors were already disclosed in patents (for example, EP 0526708 Al, WO 93/08799 Al). Accordingly, it is an object of the present invention to provide a novel therapeutics for the treatment of the above-mentioned various diseases by an invention of a novel and potent non-peptidic antagonist against either ET_A or ET_B receptor.

In order to accomplish the above object, the present inventors have developed an asymmetric conjugate addition which enables them to prepare the compound of Formula I,



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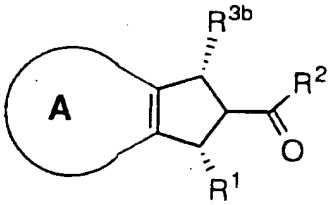
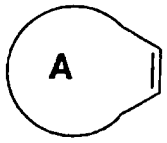
a key intermediate in the synthesis of endothelin antagonists of the following structure:



wherein



represents: 5- or 6-membered heterocyclyl, 5- or 6-membered carbocyclyl, and aryl;

R^{3b} is aryl, or heteroaryl;

R^1 is: C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, aryl, or heteroaryl;

R^2 is OR^4 and $N(R^5)_2$;

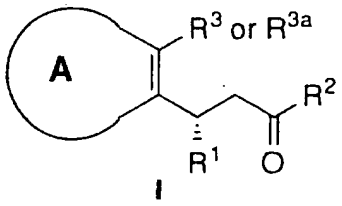
R^4 is C_1-C_8 alkyl; and

R^5 is: C_1-C_8 alkyl, or aryl.

SUMMARY OF THE INVENTION

This invention relates to a key intermediate in the synthesis of an endothelin antagonist and the synthesis of this key intermediate using an asymmetric conjugate addition reaction.

The instant invention relates to a compound of formula I:



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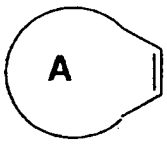
wherein



represents:

a) 5- or 6-membered heterocyclyl containing one, two or three double bonds, but at least one double bond and 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, the carbocyclyl

is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

c) aryl, wherein aryl is as defined below,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

aryl is defined as phenyl or naphthyl , which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$, and when two substituents are located on adjacent carbons they can join to form a 5- or 6-membered ring with one, two or three heteroatoms selected from O, N, and S, which is unsubstituted or substituted with with one, two or three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

n is 0 to 5;

R^1 is:

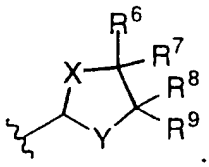
a) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl,

b) aryl, or

c) heteroaryl;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S , which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

R^2 is OR^4 or $N(R^5)_2$;

R^3 is 

;

R^{3a} is:

a) CHO,

b) -CO-C_1-C_8 alkyl,

c) -CO-aryl, or

d) -CO-heteroaryl;

X and Y are independently: O, S, or NR^5;

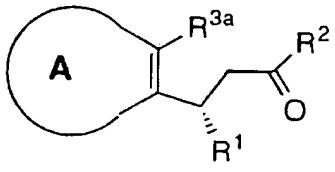
R^4 is C_1-C_8 alkyl;

R^5 is: C_1-C_8 alkyl, or aryl; and

R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3,

$N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$.

Also within the scope of the instant invention is a process for the preparation of a compound of formula I:



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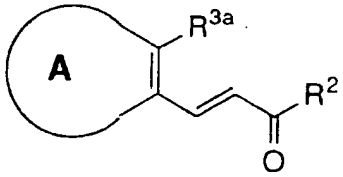
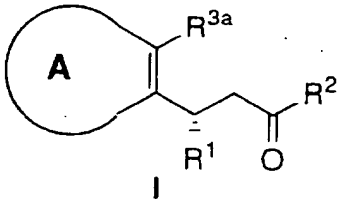
wherein the substituents are as defined above, comprising reacting a α,β-unsaturated ester or amide



with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C.

Also within the scope of the instant invention is a process for the preparation of the compound of formula I:



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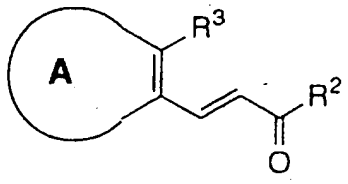
wherein the substituents are as defined above, comprising the steps of:

1) reacting an α,β-unsaturated ester or amide

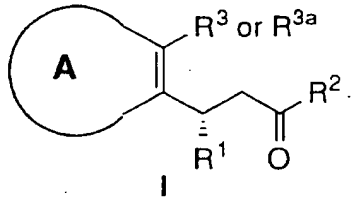


with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C to give the conjugate adduct; and

2) removing the chiral auxiliary, R^3, with aqueous acid and tetrahydrofuran to give the compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention relates to a compound of formula I:



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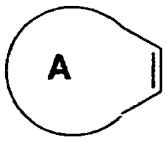
wherein



represents:

a) 5- or 6-membered heterocyclyl containing one, two or three double bonds, but at least one double bond and 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, the carbocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

c) aryl, wherein aryl is as defined below,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

aryl is defined as phenyl or naphthyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$, and when two substituents are located on adjacent carbons they can join to form a 5- or 6-membered ring with one, two or three heteroatoms selected from O, N, and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

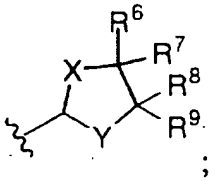
n is 0 to 5;

R^1 is:

a) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl,
b) aryl, or
c) heteroaryl;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

R^2 is OR^4 or $N(R^5)_2$;

R^3 is 

;

R^{3a} is:
a) CHO,
b) -CO-C_1-C_8 alkyl,
c) -CO-aryl, or
d) -CO-heteroaryl;

X and Y are independently: O, S, or NR^5;

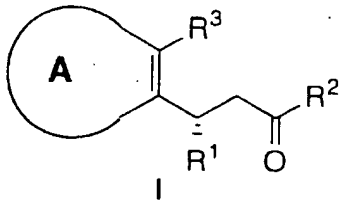
R^4 is C_1-C_8 alkyl;

R^5 is: C_1-C_8 alkyl, or aryl; and

R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to

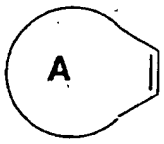
form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$.

The instant invention also relates to a process for the preparation of a compound of formula I:



I

wherein



represents:

a) 5- or 6-membered heterocyclyl containing one, two or three double bonds, but at least one double bond and 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, the carbocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8

alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

c) aryl, wherein aryl is as defined below,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

aryl is defined as phenyl or naphthyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$, and when two substituents are located on adjacent carbons they can join to form a 5- or 6-membered ring with one, two or three heteroatoms selected from O, N, and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

n is 0 to 5;

R^1 is:

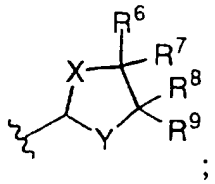
a) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl,

b) aryl, or

c) heteroaryl;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

R^2 is OR^4 or $N(R^5)_2$;

R^3 is  ;

R^{3a} is:

a) CHO,

b) -CO-C_1-C_8 alkyl,

c) -CO-aryl, or

d) -CO-heteroaryl;

X and Y are independently: O, S, or NR^5;

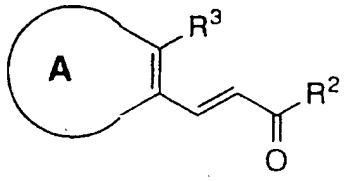
R^4 is C_1-C_8 alkyl;

R^5 is: C_1-C_8 alkyl, or aryl; and

R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8

alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$;

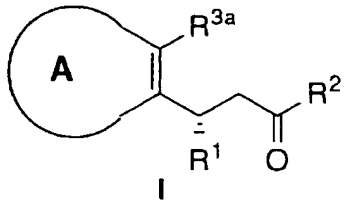
comprising reacting a α,β-unsaturated ester or amide



with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C.

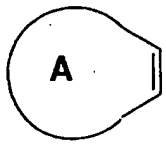
The process as recited above, wherein the number of equivalents of the organolithium compound, R^1Li, is 1 to about 4. The process as recited above, wherein the aprotic solvent is selected from the group consisting of tetrahydrofuran, diethyl ether, MTBE (methyl t-butyl ether), toluene, benzene, pentane, hexane, dioxane or a mixture of said solvents. The process as recited above, wherein the temperature range is about -78°C to about -20°C, and preferably about -78°C to about -50°C.

An embodiment of this invention is the process for the preparation of a compound of formula I:



I

wherein



represents:

a) 5- or 6-membered heterocyclyl containing one, two or three double bonds, but at least one double bond and 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, the carbocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

c) aryl, wherein aryl is as defined below,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

aryl is defined as phenyl or naphthyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$, and when two substituents are located on adjacent carbons they can join to form a 5- or 6-membered ring with one, two or three heteroatoms selected from O, N, and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

n is 0 to 5;

R^1 is:

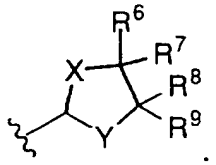
a) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl,

b) aryl, or

c) heteroaryl;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

R^2 is OR^4 or $N(R^5)_2$;

R^3 is 

;

R^{3a} is:

a) CHO,

b) -CO-C_1-C_8 alkyl,

c) -CO-aryl, or

d) -CO-heteroaryl;

X and Y are independently: O, S, or NR^5;

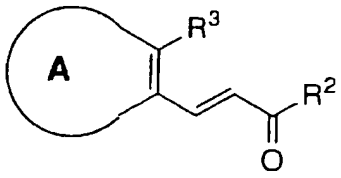
R^4 is C_1-C_8 alkyl;

R^5 is: C_1-C_8 alkyl, or aryl; and

R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$;

comprising the steps of:

1) reacting an α,β-unsaturated ester or amide



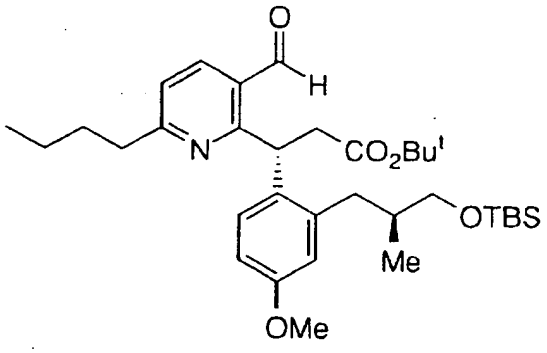
with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C to give the conjugate adduct; and

2) removing the chiral auxiliary, R^3, with aqueous acid and tetrahydrofuran to give the compound of Formula I.

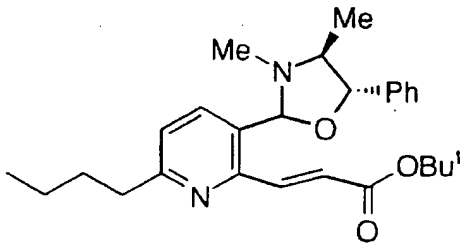
The process as recited above, wherein the number of equivalents of the organolithium compound, R^1Li, is 1 to about 4. The process as recited above, wherein the aprotic solvent is selected from the group consisting of tetrahydrofuran, diethyl ether, MTBE (methyl t-butyl ether), toluene, benzene, hexane, pentane, dioxane or a mixture of said solvents. The process as recited above, wherein the temperature

range is about -78°C to about -20°C, and preferably about -78°C to about -50°C. The process as recited above, wherein the aqueous acid is aqueous acetic acid.

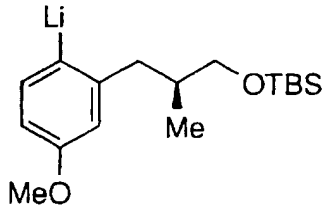
An embodiment of this invention is the process for the preparation of an aldehyde



comprising reacting an α,β-unsaturated ester or amide



with an organolithium compound

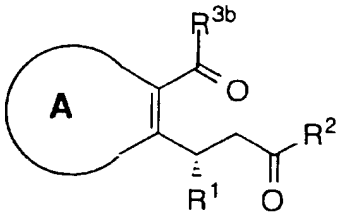


in the presence of an aprotic solvent at a temperature range of about -78°C to about -20°C.

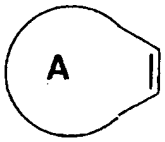
The process as recited is above, wherein the number of equivalents of the organolithium compound, R^1Li, is 1 to about 4 and preferably is 1.5 to about 2.5 equivalents. The process as recited above,

wherein the aprotic solvent is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether (MTBE), toluene, benzene, hexane, pentane, dioxane or a mixture of said solvents, and the preferable aprotic solvent is tetrahydrofuran. The process as recited above, wherein the preferred temperature range is about -78°C to about -50°C and a more preferred range is about -78°C to about -70°C.

A second embodiment of this invention is the process for the preparation of a ketone of formula:



wherein



represents:

a) 5- or 6-membered heterocyclyl containing one, two or three double bonds, but at least one double bond and 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, the carbocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8

alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

c) aryl, wherein aryl is as defined below,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

aryl is defined as phenyl or naphthyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$, and when two substituents are located on adjacent carbons they can join to form a 5- or 6-membered ring with one, two or three heteroatoms selected from O, N, and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

n is 0 to 5;

R^1 is:

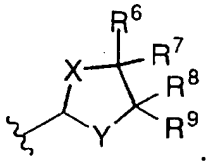
a) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl,

b) aryl, or

c) heteroaryl;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

R^2 is OR^4 or $N(R^5)_2$;

R^3 is 

;

R^{3b} is:

a) C_1-C_8 alkyl,

b) aryl, or

c) heteroaryl;

X and Y are independently: O, S, or NR^5;

R^4 is C_1-C_8 alkyl;

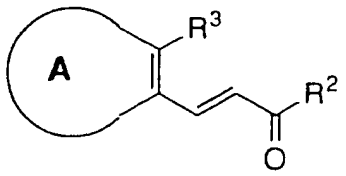
R^5 is: C_1-C_8 alkyl, or aryl; and

R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8

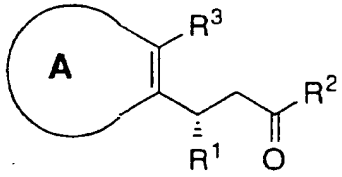
alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$;

comprising the steps of:

1) reacting a α,β-unsaturated ester or amide

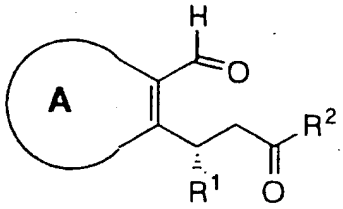


with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C to give a conjugate adduct



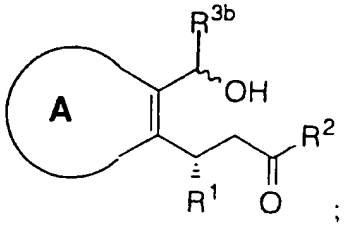
;

2) removing the chiral auxiliary with aqueous acid and tetrahydrofuran to give the aldehyde



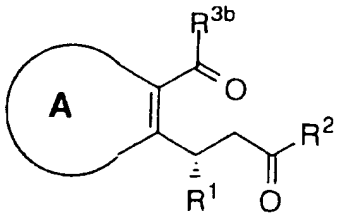
;

3) reacting the aldehyde with a Grignard reagent or organolithium reagent formed with $R^{3b}Z$, where Z is Br, Cl, or I to form an alcohol



;

4) oxidizing the alcohol formed with an oxidizing agent to give the ketone

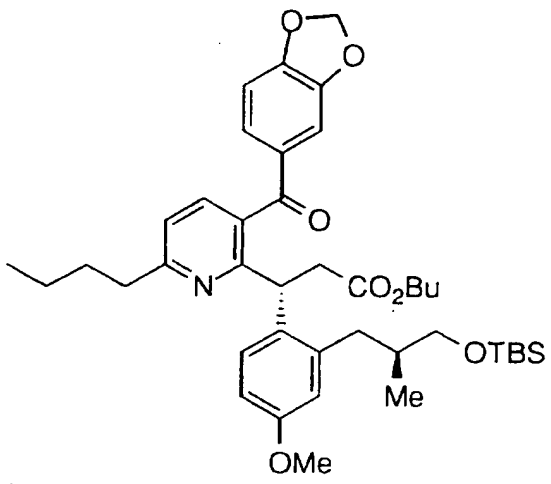


The process as recited above, wherein the number of equivalents of the organolithium compound, R^1Li, in the first step is 1 to about 4. The process as recited above, wherein the aprotic solvent in the first step is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether, toluene, benzene, pentane, hexane, dioxane or a mixture of said solvents. The process as recited above, wherein the temperature range in the first step is about -78°C to about -70°C.

The process as recited above, wherein the aqueous acid in the second step is aqueous acetic acid.

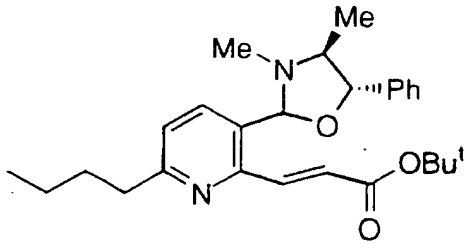
The process as recited above, wherein the oxidizing agent in the forth step is 4-methylmorpholine-N-oxide (NMO) and tetrapropylammonium perruthenate(VII) (TPAP).

A second embodiment of this invention is the process for the preparation of a ketone of formula:

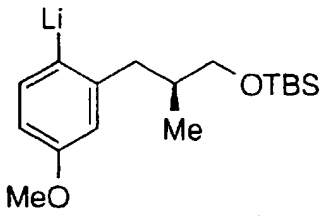


comprising the steps of:

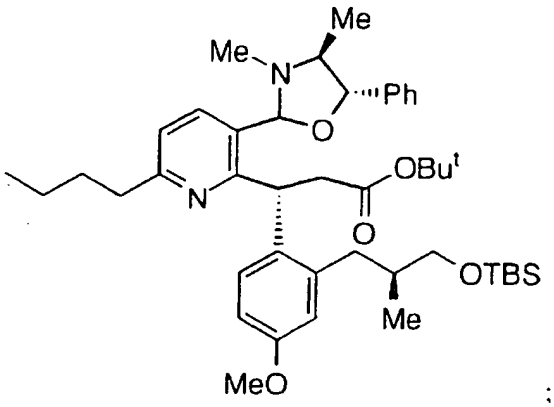
1) reacting a α,β-unsaturated ester or amide



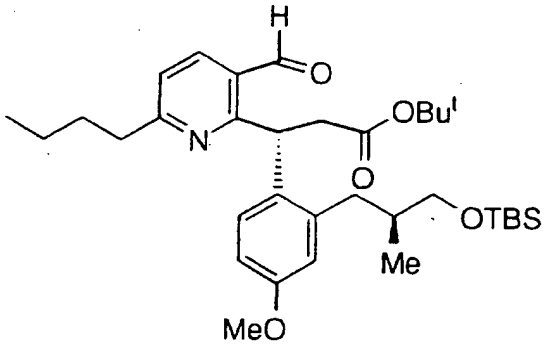
with an organolithium compound



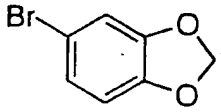
in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C to give a conjugate adduct



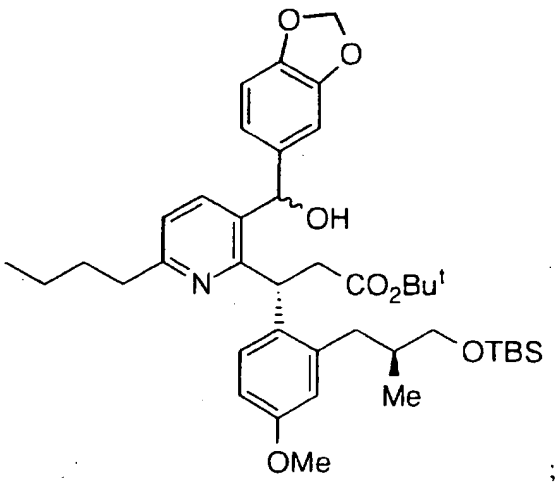
2) removing the chiral auxiliary with aqueous acid and tetrahydrofuran to give the aldehyde



3) reacting the aldehyde with a Grignard reagent or organolithium reagent formed with

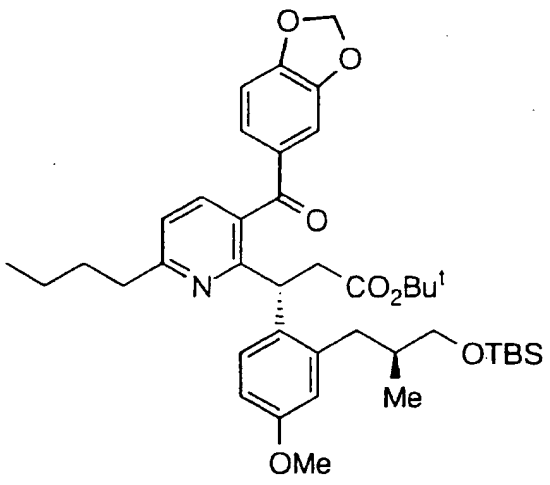


to form an alcohol



;

4) oxidizing the alcohol formed with an oxidizing agent to give a ketone



; and

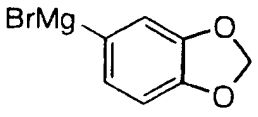
5) transesterifying the ester with n-butanol and a Lewis acid to give the desired n-butyl ester.

The process as recited above, wherein the number of equivalents of the organolithium compound, R^1Li, in the first step is 1 to about 4. The process as recited above, wherein the aprotic solvent in the first step is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether, toluene, benzene, pentane, hexane,

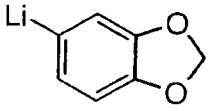
dioxane or a mixture of said solvents. The process as recited above, wherein the temperature range in the first step is about -78°C to about -50°C.

The process as recited above, wherein the aqueous acid in the second step is aqueous acetic acid.

The process as recited above, wherein the Grignard reagent or organolithium reagent in the third step are



and



, respectively.

The process as recited above, wherein the oxidizing agent in the forth step is 4-methylmorpholine-N-oxide (NMO) and tetrapropylammonium perruthenate(VII) (TPAP).

The process as recited above, wherein the fifth step is conducted in the presence of a Lewis acid selected from $Ti(OEt)_4$, $Ti(OiPr)_4$, or $Ti(OBu)_4$.

It is further understood that the substituents recited above would include the definitions recited below.

The alkyl substituents recited above denote straight and branched chain hydrocarbons of the length specified such as methyl, ethyl, isopropyl, isobutyl, tert-butyl, neopentyl, isopentyl, etc.

The alkenyl-substituents denote alkyl groups as described above which are modified so that each contains a carbon to carbon double bond such as vinyl, allyl and 2-butenyl.

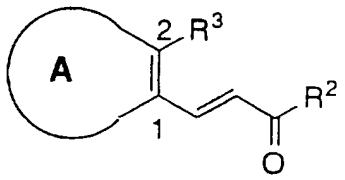
Cycloalkyl denotes rings composed of 3 to 8 methylene groups, each of which may be substituted or unsubstituted with other hydrocarbon substituents, and include for example cyclopropyl, cyclopentyl, cyclohexyl and 4-methylcyclohexyl.

The alkoxy substituent represents an alkyl group as described above attached through an oxygen bridge.

The heteroaryl substituent represents an carbazolyl, furanyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, purinyl.

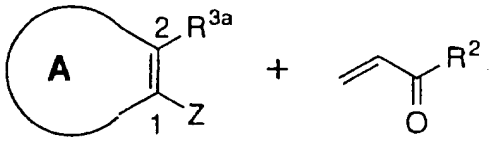
The heterocyclyl substituent represents a pyridyl, pyrimidyl, thienyl, furanyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, imidazolyl, imidazoldinyl, thiazolidilnyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrrolidinyl.

The α,β-unsaturated ester or amide



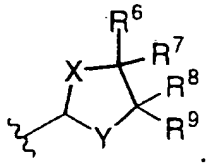
can generally be prepared in two steps:

1) a coupling reaction at the one position of Ring A



wherein Z is a leaving such as Br, Cl, I, OTriflyl, OTosyl or OMesyl and R^2 is OR^4 or $N(R^5)_2$; and

2) the conversion of the aldehyde (R^{3a}=CHO) to the desired chiral auxiliary (R^3), wherein R^3 represents

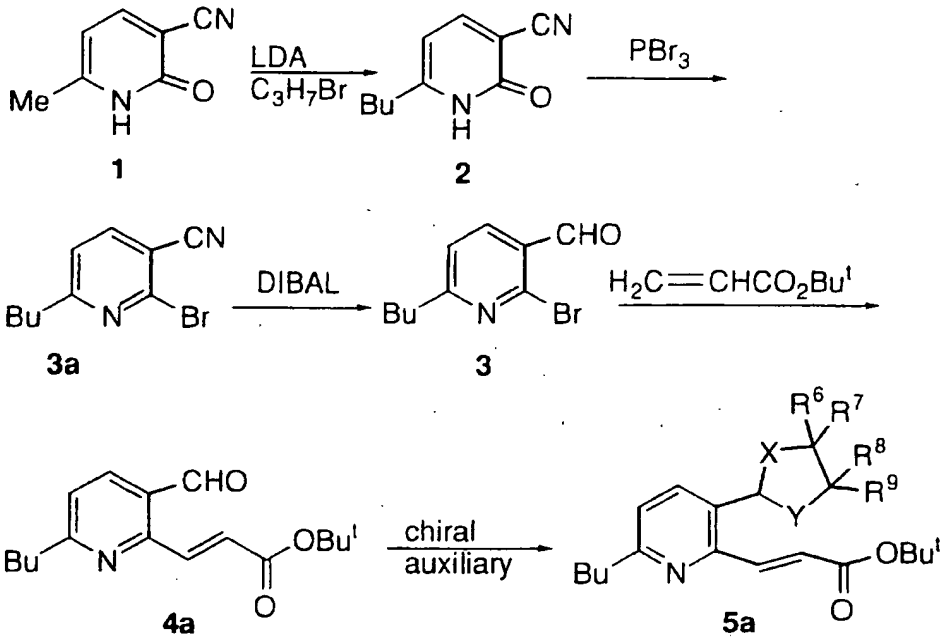


; X and Y are independently: O, S, or NR^5; R^4 is C_1-C_8 alkyl; R^5 is: C_1-C_8 alkyl, or aryl; and R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3,

$N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$.

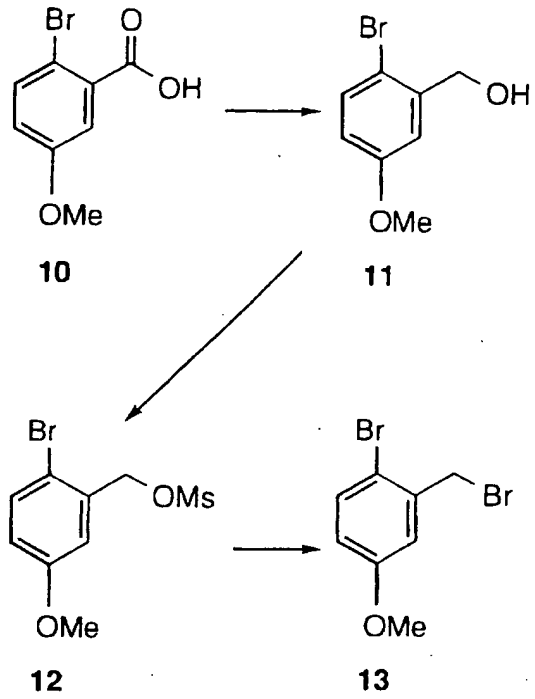
Commercially available pyridone **1** is alkylated via its dianion with propyl bromide, and the product is then converted into the bromopyridine **3a** using a brominating agent such as PBr_3. The nitrile **3a** is then reduced to the aldehyde **3** using diisobutyl aluminum hydride (DIBAL). The aldehyde then undergoes a Heck reaction with t-butyl acrylate using NaOAc, $(allyl)_2PdCl_2$, tri-o-tolylphosphine, toluene, reflux to provide the unsaturated ester **4a** in high yield. The unsaturated ester **4a** is then reacted with a chiral auxiliary to give the acceptor **5a**. Examples of chiral auxiliaries useful in this method are the enantiomers of pseudoephedrine, ephedrine, 1N,2N-dimethyl-diaminocyclohexane, diphenylprolinol, N-methylaminoindanol, and 1N,2N-diethyldiaminocyclohexane.

Scheme 1



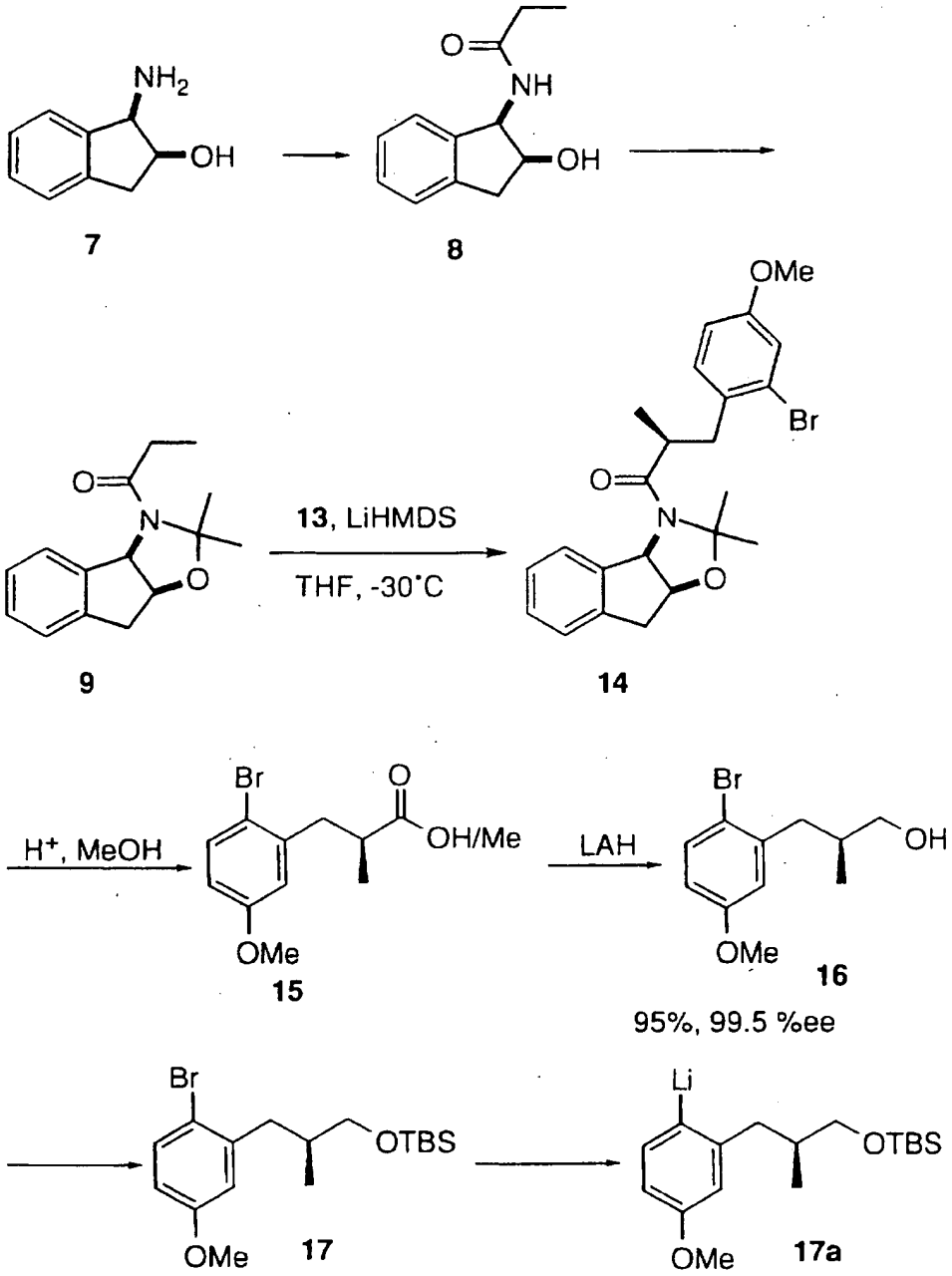
Commericially available acid **10** is reduced with $BH_3{\cdot}SMe_2$, to the alcohol **11**, which is then converted into the bromide**13**, via the mesylate **12** using mesyl chloride, triethylamine followed by the addition of NaBr and dimethylacetamide (DMAC).

Scheme 2



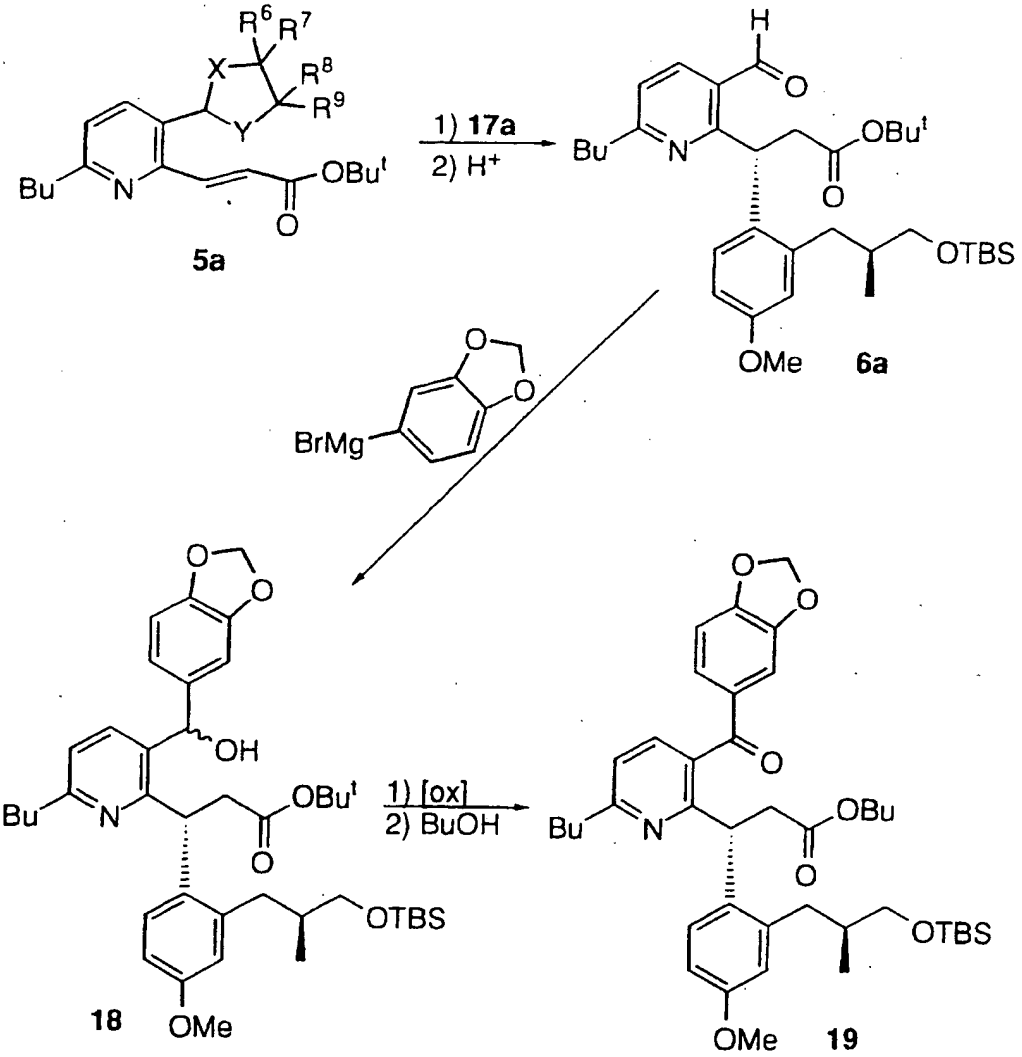
Commercial available 1,2-amino indanol is acylated (propionyl choride, K_2CO_3) to give amide **8**, which is then converted into the acetonide **9** (2-methoxypropene, pyridinium p-toluene-sulfonate (PPTS)). Acetonide **9** is then alkylated with the bromide **13**, (LiHMDS) to give **14**, which is then hydrolyzed (H^+, MeOH) to give a mixture of acid and methyl ester **15**. Reduction (LAH) of the ester/acid mixture provided the alcohol **16** in high yield and optical purity. Protection of the alcohol **16** (TBSCl, imidazole) provided bromide **17**, the precursor to organolithium **17a**.

Scheme 3


NH2
OH
7
O
NH
OH
8
OMe
Br
O
N
O
13, LiHMDS
THF, -30°C
9
14
H+, MeOH
Br
O
OH/Me
OMe
15
LAH
Br
OH
OMe
16
95%, 99.5 %ee
Br
OTBS
OMe
17
Li
OTBS
OMe
17a

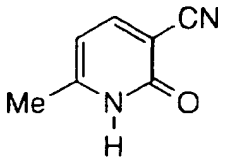
Compound **17a** is added to the α,β-unsaturated ester **5a** at -78° to -50°C. Work up with acetic acid, THF and water (to remove the auxiliary) affords compound **6a** in high yield and good selectivity. Addition of the Grignard leads to compound **18**. Oxidation with reagents such as NMO and TPAP with molecular sieves, followed by transesterification in n-butanol with $Ti(OBu)_4$ leads to compound **19** in good yield.

Scheme 4



The instant invention can be understood further by the following examples, which do not constitute a limitation of the invention.

EXAMPLE 1

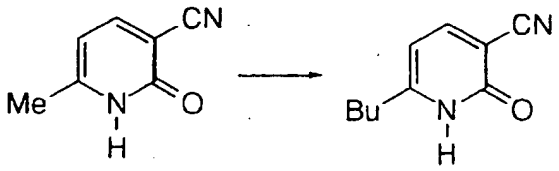


1

Preparation of 1

Compound 1 is a commericially available starting material, for example, see Aldrich Chemical Company, Milwaukee, WI, USA 53201.

EXAMPLE 2

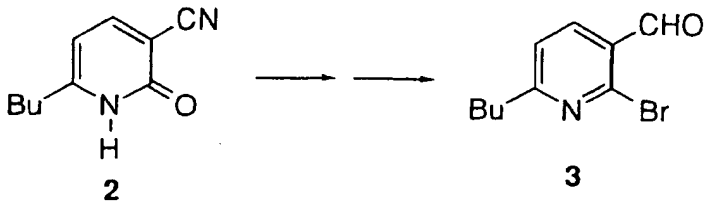


1 2

Preparation of 2

Diisopropyl amine (MW 101.19, d 0.772, 2.1 equ, 20.54 mL) in 200 mL THF. Cool to -50°C and add n-BuLi (1.6 M in hexanes, 2.05 equ, 96 mL), allowing solution to warm to -20°C. Age 0-3°C for 15 min, then cool to -30°C and add **1** (MW 134.14, 75 mmol, 10.0 g). Age 0°C to 43°C for 2 h. Cool to -50°C and add bromopropane (MW 123.00, d 1.354, 1.0 equ, 6.8 mL). Warm to 25°C over 30 min, and age 30 min. Add NH_4Cl and CH_2Cl_2. Dry organic (magnesium sulfate) then evaporate *in vacuo* to afford 61% of **2**.

EXAMPLE 3



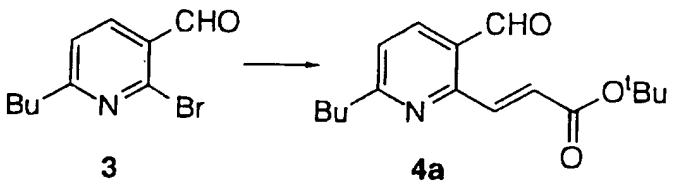
2 3

Preparation of 3

Mix 2 (MW 176.22, 46 mmol) and PBr_3 (MW 270.70, d 2.880, 2.5 equ, 10.8 mL) and age at 160°C. After 2 h, cool to 25°C and add some CH_2Cl_2. Slowly quench by adding water. Separate layers and wash aqueous two times with CH_2Cl_2. Combine organic layers and dry (magnesium sulfate). Concentrate and isolate solid by silica gel chromatography (90:10 hexanes:ethyl acetate) in 60% yield (MW 239.12, 6.60 g).

Dissolve product of bromination reaction (MW 239.12, 27.6 mmol, 6.60 g) in 66 mL toluene and cool to -42°C. Slowly add DIBAL (1.5 M in toluene, 2 equ, 37 mL) and age 1 h at -42°C. Add HCl (2 N, 10 equ, 134 mL) and stir vigorously for 30 min. Dilute with ethyl acetate, separate layers, and wash aqueous with ethyl acetate. Combine organic layers, dry (magnesium sulfate), and concentrate *in vacuo* to afford 90% (MW 242.11, 6.01 g) of **3**.

EXAMPLE 4a

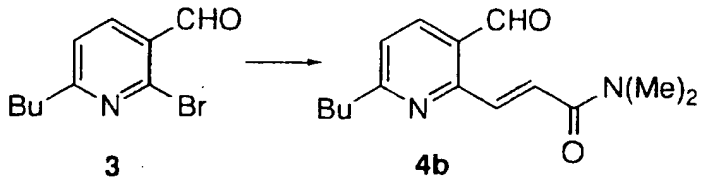


3 4a

Preparation of **4a**

Dissolve **3** (MW 242.11, 24.8 mmol, 6.01 g) in 75 mL toluene. Add sodium acetate (MW 82, 3 equ, 6.13 g), t-butyl acrylate (MW 128.17, d 0.875, 2.5 equ, 9.08 mL), P(o-tolyl)3 (MW 304.38, 10 mol %, 755 mg) and allyl palladium chloride dimer (MW 365.85, 5 mol %, 455 mg). Age at reflux for 24 h. Cool, filter and evaporate *in vacuo*. Isolate **4a** (MW 289.37) by silica gel chromatography (92:8 hexanes:ethyl acetate) in 80% yield (5.74 g).

EXAMPLE 4b

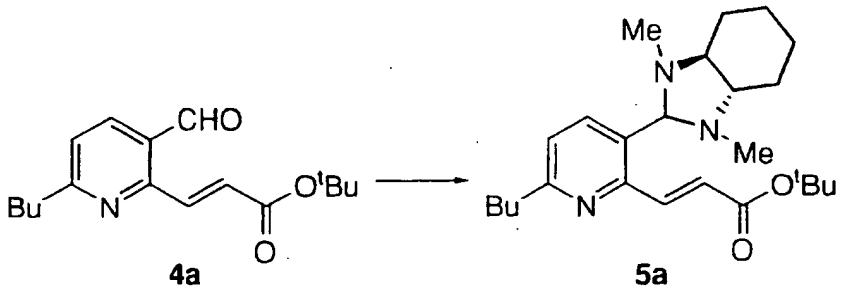


3 **4b**

Preparation of **4b**

Dissolve **3** (MW 242.11, 24.8 mmol, 6.01 g) in 75 mL toluene. Add sodium acetate (MW 82, 3 equ, 6.13 g), dimethylacrylamide (MW 99.13, d 0.962, 1 equ, 2.55 mL), PPh3 (MW 262.29, 10 mol %, 653 mg) and allyl palladium chloride dimer (MW 365.85, 5 mol %, 455 mg). Age at 140°C in sealed tube for 24 h. Cool, filter and evaporate *in vacuo*. Isolate **4b** (MW 260.34) by silica gel chromatography (80:20 hexanes:ethyl acetate) in 70% yield (4.52 g).

EXAMPLE 5a

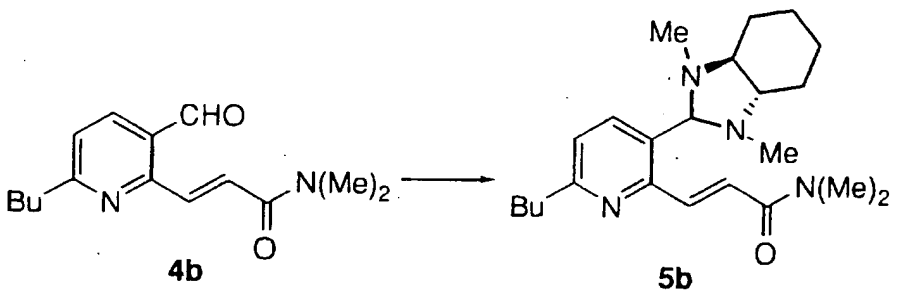


4a **5a**

Preparation of **5a**

Dissolve **4a** (MW 289.37, 19.8 mmol, 5.74 g) in 53 mL CH_2Cl_2. Add (1R,2R)-N,N-dimethylcyclohexanediamine (MW 142.24, 1 equ, 2.83 g) and sieves (powdered, 1 wt equ, 5.74 g) and age 25°C for 8 h. Filter and concentrate filtrate *in vacuo* to afford **5a** (MW 413.60, 8.19 g) in quantitative yield.

EXAMPLE 5b

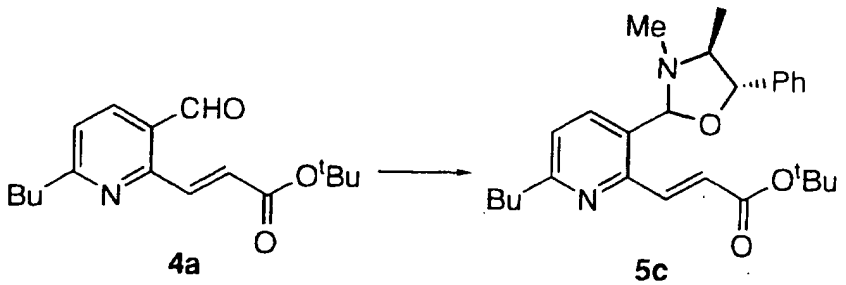


4b **5b**

Preparation of **5b**

Dissolve **4b** (MW 260.34, 17.4 mmol, 4.53 g) in 40 mL CH_2Cl_2. Add (1R,2R)-N,N-dimethylcyclohexanediamine (MW 142.24, 1 equ, 2.47 g) and sieves (powdered, 1 wt equ, 4.53 g) and age 25°C for 8 h. Filter and concentrate filtrate *in vacuo* to afford **5b** (MW 384.57, 6.69 g) in quantitative yield.

EXAMPLE 5c

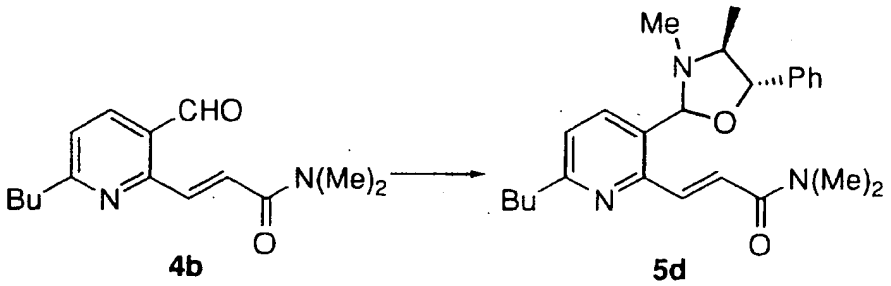


4a **5c**

Preparation of **5c**

Dissolve **4a** (MW 289.37, 19.8 mmol, 5.74 g) in 53 mL toluene. Add (S,S)-pseudoephedrine (MW 165.24, 1.1 equ, 3.60 g) and 4 drops of concentrated HCl. Reflux with a Dean-Stark trap for 2h. Wash with saturated aqueous $NaHCO_3$ and extract with ethyl acetate. Dry organic layer with $MgSO_4$, then filter and concentrate filtrate *in vacuo* to afford **5c** (MW 4436.59, 8.64 g) in quantitative yield. ^1H NMR ($CDCl_3$) : 8.23 (d, J=11.78, 1 H), 7.88 (d, J=7.33, 1 H), 7.39 (m, 5 H), 7.16 (d, J=7.33, 1 H), 7.02 (d, J=11.78, 1 H), 5.31 (s, 1 H), 4.80 (d, J=9.18, 1 H), 2.80 (t, J=5.79, 2 H), 2.59 (m, 1 H), 2.19 (s, 3 H), 1.72 (m, 2 H), 1.56 (s, 9 H), 1.39 (m, 2 H), 1.27 (d, J=4.83, 3 H), 0.94 (t, J=6.76, 3 H).

EXAMPLE 5d

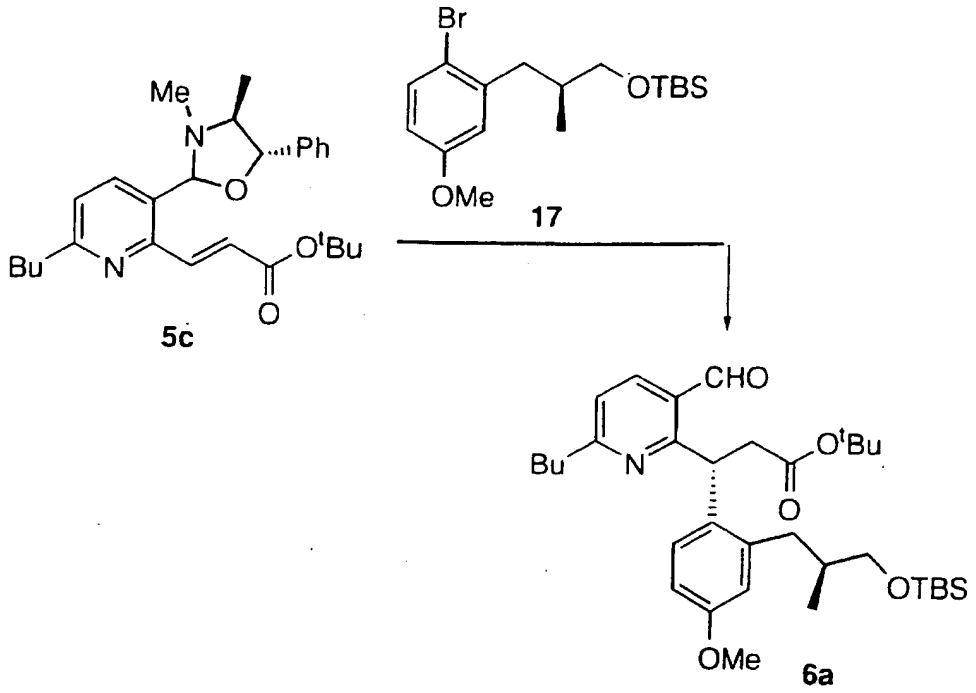


4b **5d**

Preparation of **5d**

Dissolve **4b** (MW 260.34, 117.4 mmol, 5.74 g) in 53 mL toluene. Add (S,S)-pseudoephedrine (MW 165.24, 1.1 equ, 3.16 g) and 4 drops of concentrated HCl. Reflux with a Dean-Stark trap for 2h. Wash with saturated aqueous $NaHCO_3$ and extract with ethyl acetate. Dry organic layer with $MgSO_4$, then filter and concentrate filtrate *in vacuo* to afford **5c**.

EXAMPLE 6a

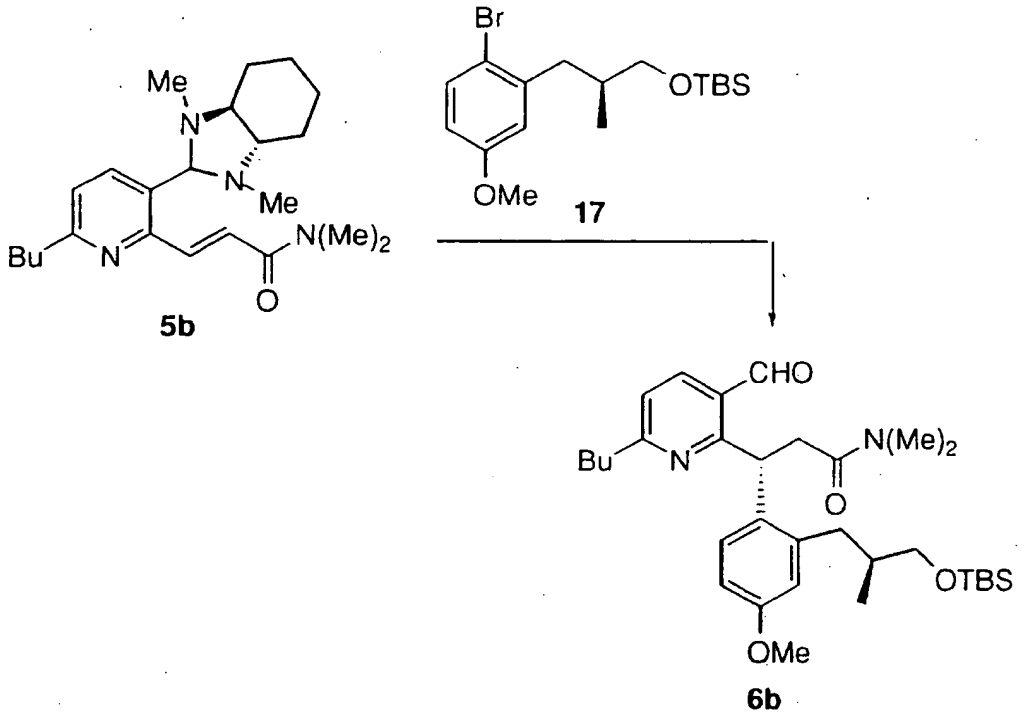


Preparation of **6a**

Dissolve **17** (see Example 17, MW 373.41, 2 equ, 14.79 g) in 85 mL THF. Cool to -78°C and add t-BuLi (1.7 M in pentane, 4 equ, 46.6 mL), maintaining temperature below -70°C. Age 15 min, then slowly add solution of **5c** (MW 436.59, 19.8 mmol, 8.64 g) in 65 mL THF. Age 1 h at -78°C, then cannula into cold aq NH_4Cl (100 mL). Add ethyl acetate and separate layers. Wash aqueous with ethyl acetate. Combine organic layers and wash with brine, then dry (magnesium sulfate) and evaporate *in vacuo*. ^1H NMR provides de data. Add THF (75 mL), acetic acid (AcOH) (30 mL) and water (10 mL). Age 5 h at 25°C. Separate layers and wash aqueous two times with ethyl acetate. Combine organic layers, wash with brine, dry (magnesium sulfate), and evaporate *in vacuo*. **6a** (MW 583.89) is isolated in 85% yield (9.83 g) by silica gel chromatography (92:8 hexanes:ethyl acetate).

^{1}H NMR (C_6D_6) : 10.5 (s, 1 H), 7.72 (d, *J*=7.85, 1 H), 7.30 (d, *J*=8.64, 1 H), 6.83 (d, *J*=8.05, 1 H), 6.59 (dd, *J*=8.65, 2.61, 1 H), 6.56 (d, *J*=7.99, 1 H), 5.92 (m, 1 H), 3.85 (dd, *J*=16.32, 10.77, 1 H), 3.48 (m, 2 H), 3.32 (s, 3 H), 3.01 (dd, *J*=14.11, 6.77, 1 H), 2.87 (dd, *J*=16.30, 3.91, 1 H), 2.79 (dd, *J*=13.25, 6.21, 1 H), 2.68 (t, *J*=7.66, 2 H), 2.10 (m, 1 H), 1.72 (m, 2 H), 1.30 (s, 9 H), 1.25 (m, 2 H), 1.01 (s, 9 H), 0.95 (d, *J*=6.42, 3 H), 0.94 (t, *J*=8.40, 3 H), 0.10 (d, *J*=5.83, 6 H).

EXAMPLE 6b



Preparation of **6b**

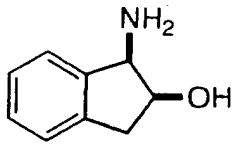
Dissolve **17** (see Example 17, MW 373.41, 2 equ, 12.99 g) in 70 mL THF. Cool to -78°C and add t-BuLi (1.7 M in pentane, 4 equ, 40.9 mL), maintaining temperature below -70°C. Age 15 min, then slowly add solution of **5b** (MW 384.57, 17.4 mmol, 6.69 g) in 55 mL THF. Age 1 h at -78°C, then cannula into cold aq NH_4Cl (100 mL). Add ethyl acetate and separate layers. Wash aqueous with ethyl acetate.

Combine organic layers and wash with brine, then dry (magnesium sulfate) and evaporate *in vacuo*. ^{1}H NMR provides de data. Add THF (55 mL), AcOH (20 mL) and water (8 mL). Age 5 h at 25°C. Separate layers and wash aqueous two times with ethyl acetate. Combine organic layers, wash with brine, dry (magnesium sulfate), and evaporate *in vacuo*. **6b** (MW 678.99) is isolated in 75% yield (8.86 g) by silica gel chromatography (70:30 hexanes:ethyl acetate).

^{1}H NMR ($CDCl_3$) : 10.30 (s, 1 H), 7.99 (d, *J*=4.74, 1 H), 7.11 (d, *J*=3.19, 1 H), 6.89 (d, *J*=8.61, 1 H), 6.78 (d, *J*=2.76, 1 H), 6.59 (t, *J*=2.78, 1 H), 5.70 (t, *J*=2.86, 1 H), 3.87 (dd, *J*=11.18, 4.29, 1 H), 3.74 (s, 3 H), 3.58 (m, 2 H), 3.11 (s, 3 H), 3.25 (dd, *J*=14.35, 6.25, 1 H), 2.88 (s, 3 H), 2.84 (m, 2H), 2.68 (dd, *J*=14.35, 8.30, 1 H), 2.47 (dd, *J*=9.02, 2.89, 1 H), 2.09 (m, 1 H), 1.75 (m, 2 H), 1.39 (m, 2 H), 0.99 (t, *J*=3.49, 3 H), 0.92 (s, 9 H), 0.92 (d, *J*=7.15, 6 H), 0.08 (d, *J*=1.91, 6 H).

^{13}C NMR ($CDCl_3$) : 190.5, 171.6, 165.9, 163.7, 157.9, 139.3, 137.2, 135.5, 130.0, 127.1, 120.8, 115.5, 111.7, 67.8, 55.11, 39.7, 38.9, 38.4, 37.2, 36.8, 36.0, 35.4, 26.0 (3 C), 22.3, 18.4, 17.3, 14.7, -5.3 (2 C).

EXAMPLE 7

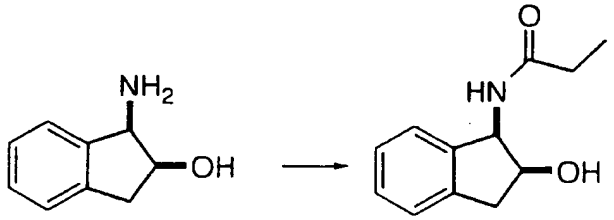


7

Preparation of 7

Compound 7 is a commericially available starting material, for example, see DSM Andeno, Grubbenvorsterweg 8, P.O. Box 81, 5900 AB Venlo,The Netherlands.

EXAMPLE 8

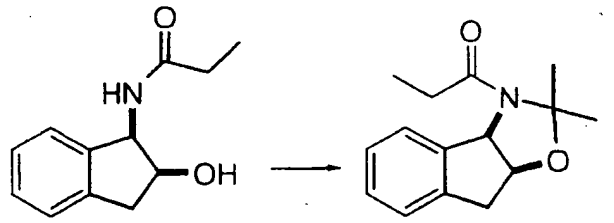


7 8

Preparation of **8**

Na_2CO_3 (MW 105.99, 1.5 equ, 8.8 g) dissolved in 82 mL water. Add a solution of (1R,2S) amino indanol **7** (MW 149.19, 55.0 mmol, 8.2 g) in 160 mL CH_2Cl_2. Cool to -5°C and add propionyl chloride (MW 92.53, d 1.065, 1.3 equ, 6.2 mL). Warm to 25°C and age 1 h. Separate layers and dry organic (magnesium sulfate). Concentrate *in vacuo* to afford **8** (MW 205.26, 10 g) in 89% isolated yield.

EXAMPLE 9



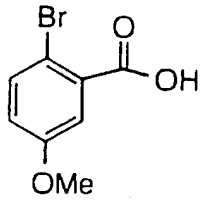
8 9

Preparation of **9**

To a solution of **8** (MW 205.26, 49.3 mmol, 10 g) in 200 mL THF, add pyridinium *p*-toluenesulfonate (PPTS) (MW 251.31, 0.16 equ, 2g) then methoxypropene (MW 72.11, d 0.753, 2.2 equ, 10.4 mL). Age 2 h at 38°C, then add aqueous sodium bicarbonate and ethyl acetate.

The organic layer was dried (magnesium sulfate). After concentration *in vacuo*, **9** (MW 245.32, 12.09 g) was formed in quantitative yield.

EXAMPLE 10

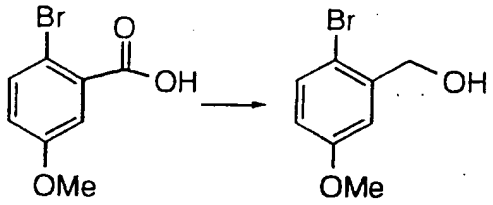


10

Preparation of **10**

Compound 10 is a commericially available starting material, for example, see Lancaster Synthesis, P.O. Box 1000, Windham, NH 03087-9977 or Ryan Scientific, Inc., P.O. Box 845, Isle of Palms, SC 29451-0845.

EXAMPLE 11

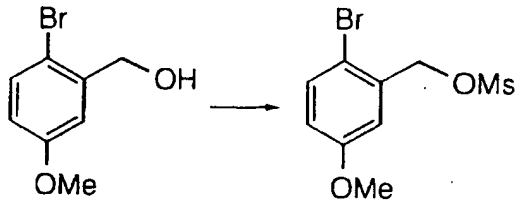


10 **11**

Preparation of **11**

10 (MW 231.05, 130 mmol, 30.0 g) in 300 mL CH_2Cl_2 at 0°C. Add BH_3-SMe_2 (3 equ, 25.2 mL) and age for 2 h at 25°C. Quench into aqueous 2 N HCl and separate layers. Dry organic (magnesium sulfate) and concentrate *in vacuo* to obtain 94% yield of **11** (MW 217.06, 25.5 g).

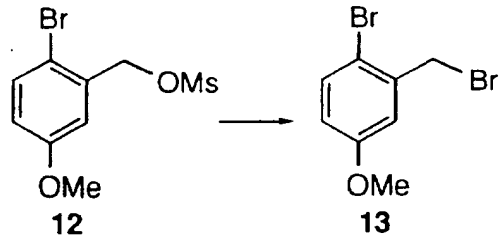
EXAMPLE 12



Preparation of **12**

Dissolve **11** (MW 217.06, 47.2 mmol, 10.24 g) in 55 mL CH_2Cl_2 and cool to -20°C. Add DIEA (MW 129.25, d 0.742, 1.3 equ, 10.69 mL) then methane sulfonyl chloride (MsCl) (MW 114.55, d 1.480, 1.2 equ, 4.38 mL). Age -5°C to 0°C for 1 h then quench into 55 mL water. Extract with CH_2Cl_2 then wash with 1N H_2SO_4 (40 mL), then brine. Dry organic layers (magnesium sulfate) and concentrate *in vacuo* to afford **12** (MW 295.15, 13.23 g) in 95% yield.

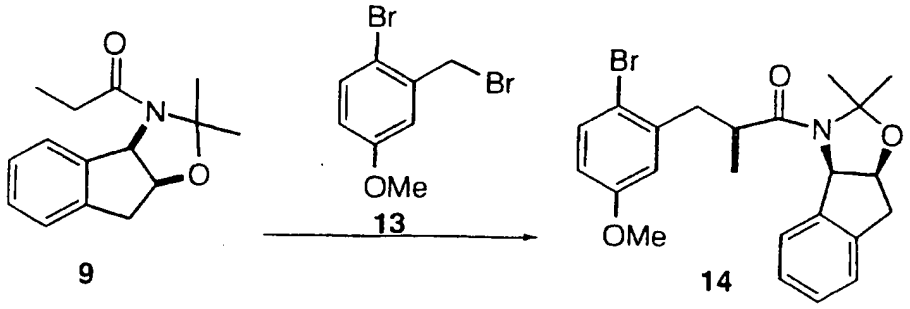
EXAMPLE 13



Preparation of **13**

12 (MW 295.15, 44.8 mmol, 13.23 g) in 44 mL dimethylacetamide (DMAC). Add NaBr (MW 102.90, 2 equ, 9.22 g) and age 1h. Add 88 mL water and collect solid by filtration. Wash cake with water and dry by suction. Quantitative yield of **13** (MW 279.96, 12.54 g) is obtained.

EXAMPLE 14

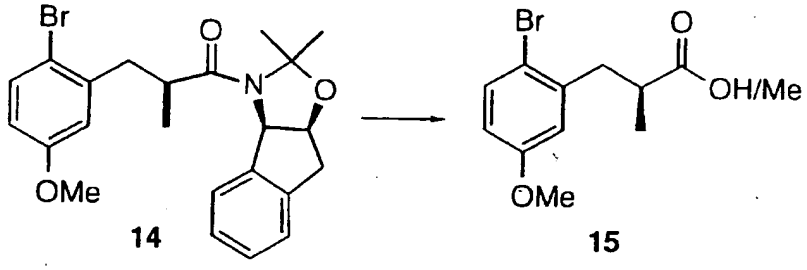


9 14

Preparation of **14**

9 (MW 245.32, 1.1 equ, 89.1 g) in 1 L THF, cooled to -50°C. Add LiHMDS (1.0 M in THF, 1.5 equ, 545 mL) and age 1.5 h, warming to -30°C. Add **13** (MW 279.96, 327 mmol, 91.3 g) in 300 mL THF, and age -35°C for 1 h. Warm to -10°C over 1 h, then quench into aqueous NH_4Cl. Separate layers and extract with ethyl acetate. Dry organic and concentrate *in vacuo* to afford crude **14** (MW 444.37).

EXAMPLE 15



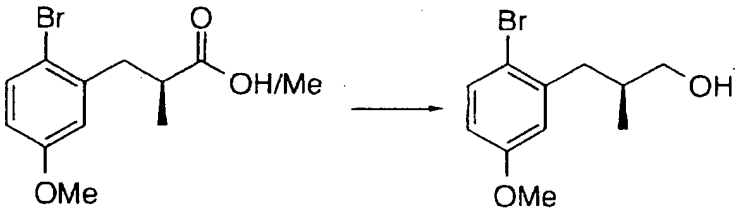
14 15

Preparation of **15**

14 in 1 L MeOH and cooled to 10°C. Bubble in HCl gas for 1 h until reaction is complete. 2 L H_2O added and the product was filtered. The cake was washed with H_2O and dried to give the product

hydroxyamide, which was then dissolved in 1 L MeOH and 1.5 L 6N HCl and refluxed overnight. The mixture was cooled to 25°C and extracted with CH_2Cl_2 to give, after concentration, compounds **15** (60 g, 64% from bromide **13**).

EXAMPLE 16

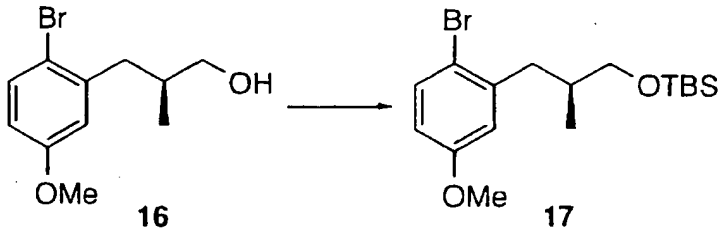


15 **16**

Preparation of **16**

15 (mixture of acid and ester, 26.88 mmol) in 150 mL THF at -78°C. Add lithium aluminum hydride ($LiAlH_4$) (1 M in THF, 2 equ, 53.76 mL) over 30 min. Warm to 25°C over 1 h, then quench into aqueous NH_4Cl. Add ethyl acetate, extract ethyl acetate. Wash organics with brine, dry (magnesium sulfate), and concentrate *in vacuo* to afford 95% yield of **16** (MW 259.14, 6.62 g).

EXAMPLE 17



16 **17**

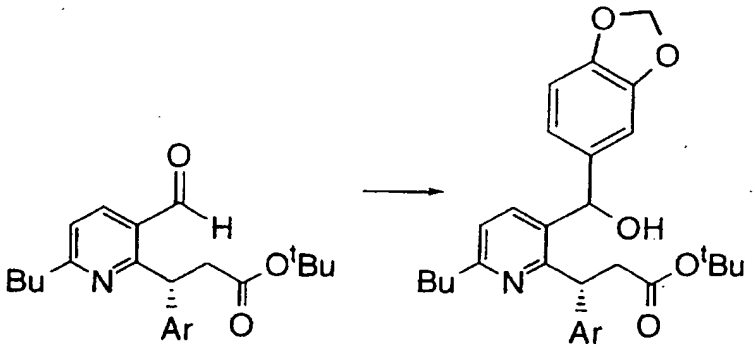
Preparation of **17**

16 (MW 259.14, 25.54 mmol, 6.62 g) in 35 mL CH_2Cl_2 and cool to 0°C. Add imidazole (MW 68.08, 2.5 equ, 4.35 g) and then tert-butyldimethylsilyl chloride (TBSCl) (MW 150.73, 1 equ, 3.85 g). Age 1 h at 25°C then quench with aqueous $NaHCO_3$ and add ethyl acetate. Extract with ethyl acetate, then dry organic layer (magnesium sulfate) and concentrate *in vacuo* to afford a quantitative yield of **17** (MW 373.41, 9.54 g).

^1H NMR ($CDCl_3$) : 7.41 (d, *J*=8.74, 1H), 6.77 (d, *J*=3.04, 1H), 6.63 (dd, *J*=8.73, 3.06, 1H), 3.78 (s, 3 H), 3.50 (d, *J*=5.75, 2 H), 2.89 (dd, *J*=13.31, 6.15, 1 H), 2.45 (dd, *J*=13.30, 8.26, 1 H), 2.03 (m, 1 H), 0.94 (s, 9 H), 0.92 (d, *J*=5.01, 3 H), 0.07 (s, 6 H).

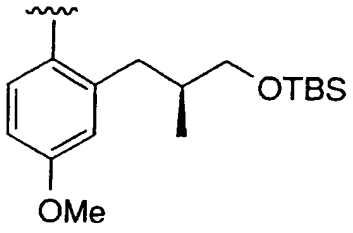
^{13}C NMR ($CDCl_3$) : 159.1, 141.6, 133.2, 117.0, 115.4, 113.2, 67.4, 55.4, 39.7, 36.3, 26.0 (3C), 18.4, 16.5, -5.3 (2C).

EXAMPLE 18



6a **18**

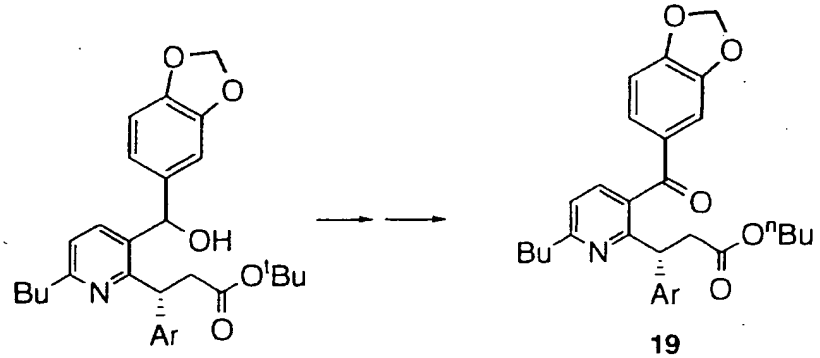
Ar represents:



Preparation of **18**

Prepare 0.5 M Grignard solution from 4-bromo-1,2-(methylenedioxy)benzene (MW 201.01, 42.1 mmol, 8.46 g) and Mg (MW 24.31, 1.5 equ, 1.54 g) in 84 mL THF. Dissolve **6a** (MW 583.89, 16.8 mmol, 9.83 g) in 80 mL THF and cool to -78°C. Slowly add Grignard solution (2.5 equ, 0.5 M, 84 mL) and age 30 min. Quench into aqueous NH_4Cl and add ethyl acetate. Wash organic with brine, dry (magnesium sulfate) and evaporate *in vacuo*. Carry crude into oxidation.

EXAMPLE 19



18 **19**

Preparation of **19**

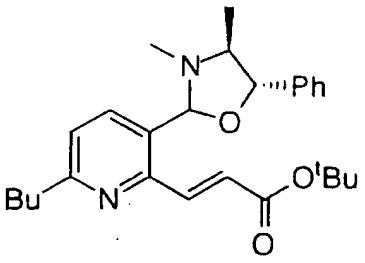
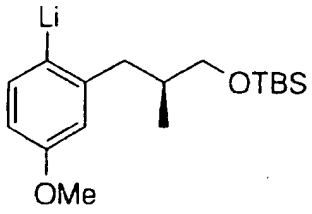
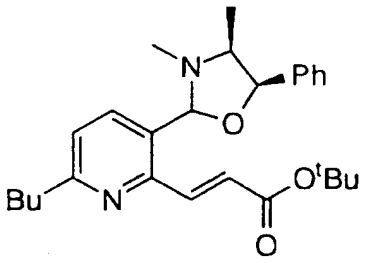
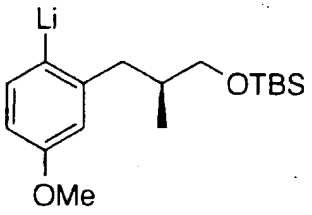
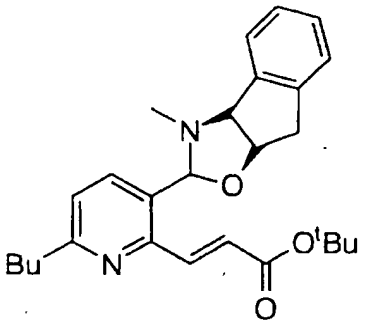
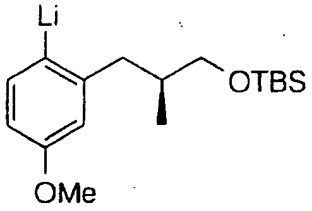
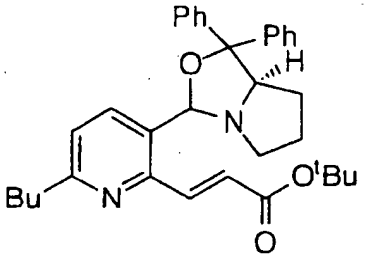
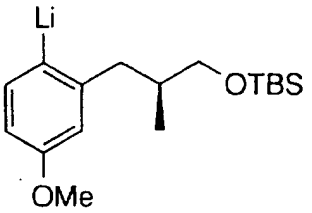
Crude **18** (MW 706.01, 16.8 mmol) in 150 mL ACN. Add NMO (MW 117.15, 3 equ, 5.90 g), sieves (powdered, 3 wt equ, 35.6 g), and TPAP (MW 351.43, 10 mol %, 590 mg) and age 25°C for 2 h. Concentrate to remove ACN, then elute through silica gel pad with ethyl acetate. Concentrate *in vacuo*, then chromatograph (90:10 hexanes:ethyl acetate) to isolate the oxidation product (85% yield over two steps).

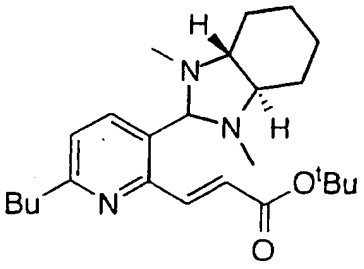
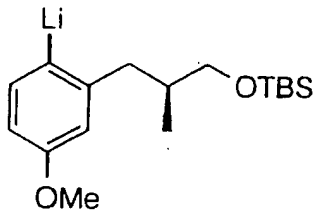
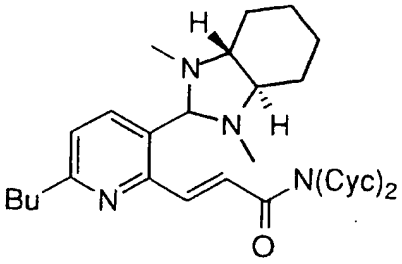
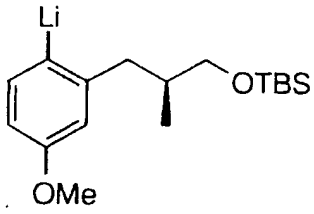
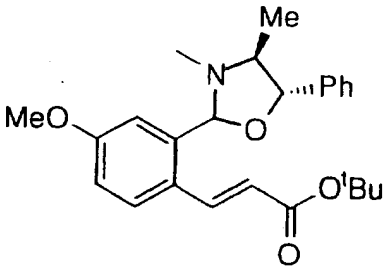
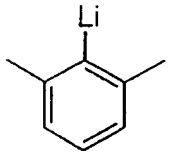
Dissolve in 100 mL n-BuOH and add $Ti(OBu)_4$ (MW 340.366, 5 equ, 28.59 g). Reflux for 48 h, then quench into water and add ethyl acetate. Filter through celite, separate the layers, and wash the

organic with brine. Dry (magnesium sulfate) and evaporate *in vacuo* to afford 81% yield (over three steps) of **19** (MW 703.99, 9.58 g).

EXAMPLES 20-26

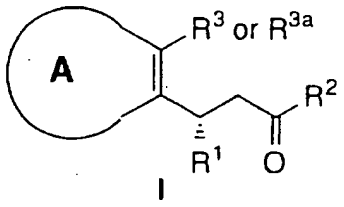
Following the procedures described in Examples 6a and 6b, the nucleophiles were added to the acceptors listed below and the diastereomeric ratios (%de) of the products were determined by evaluation of the ^{1}H NMR data and are shown below.

Ex.	Acceptor	Nucleophile	%de
20			90%
21			65%
22			88%
23			50%

Ex.	Acceptor	Nucleophile	%de
24			76%
25			92%
26			88%

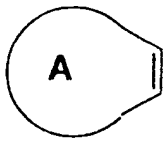
WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

wherein



represents:

a) 5- or 6-membered heterocyclyl containing one, two or three double bonds, but at least one double bond and 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, the carbocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

c) aryl, wherein aryl is as defined below,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy,

C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

aryl is defined as phenyl or naphthyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$, and when two substituents are located on adjacent carbons they can join to form a 5- or 6-membered ring with one, two or three heteroatoms selected from O, N, and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

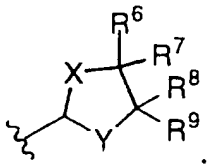
n is 0 to 5;

R^1 is:

a) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl,
b) aryl, or
c) heteroaryl;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

R^2 is OR^4 or $N(R^5)_2$;

R^3 is  ;

R^{3a} is:

a) CHO,
b) -CO-C_1-C_8 alkyl,
c) -CO-aryl, or
d) -CO-heteroaryl;

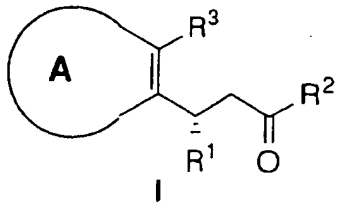
X and Y are independently: O, S, or NR^5;

R^4 is C_1-C_8 alkyl;

R^5 is: C_1-C_8 alkyl, or aryl; and

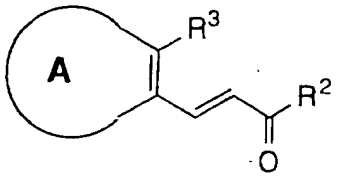
R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$.

2. A process for the preparation of a compound of formula I:



I

wherein the compound of formula I is as defined in Claim 1, comprising reacting a α,β-unsaturated ester or amide



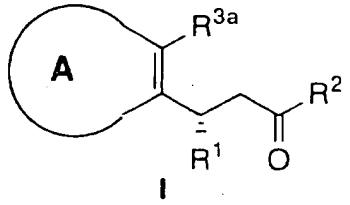
with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C.

3. The process as recited in Claim 2, wherein the number of equivalents of the organolithium compound, R^1Li, is 1 to about 4.

4. The process as recited in Claim 3, wherein the aprotic solvent is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether, benzene, toluene, hexane, pentane, dioxane and a mixture of said solvents.

5. The process as recited in Claim 4, wherein the temperature range is about -78°C to about -20°C.

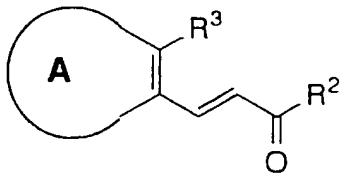
6. A process for the preparation of a compound of formula I:



I

wherein the compound of formula I is as defined in Claim 1, comprising the steps of:

1) reacting an α,β-unsaturated ester or amide



with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C to give the conjugate adduct; and

2) removing the chiral auxiliary, R^3, with aqueous acid and tetrahydrofuran to give the compound of Formula I.

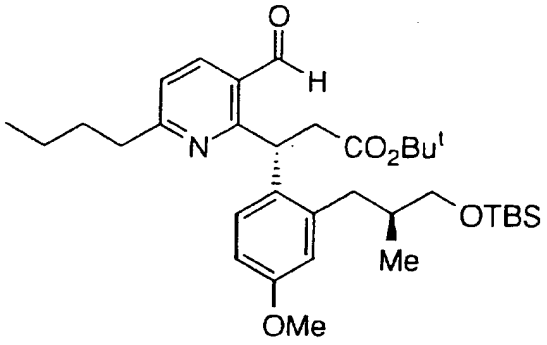
7. The process as recited in Claim 6, wherein the number of equivalents of the organolithium compound, R^1Li, is 1 to about 4.

8. The process as recited in Claim 7, wherein the aprotic solvent is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether, benzene, toluene, hexane, pentane, dioxane and a mixture of said solvents.

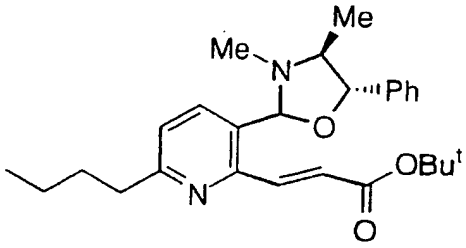
9. The process as recited in Claim 8, wherein the temperature range is about -78°C to about -20°C.

10. The process as recited in Claim 9, wherein the aqueous acid is aqueous acetic acid.

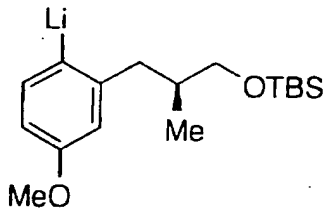
11. A process for the preparation of



comprising reacting a α,β-unsaturated ester or amide



with an organolithium compound



in the presence of an aprotic solvent at a temperature range of about -78°C to about -20°C.

12. The process as recited in Claim 11, wherein the number of equivalents of the organolithium compound, R^1Li, is 1 to about 4.

13. The process as recited in Claim 12, wherein the aprotic solvent is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether, benzene, toluene, pentane, hexane, dioxane and a mixture of said solvents.

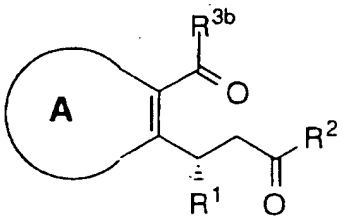
14. The process as recited in Claim 13, wherein the temperature range is about -78°C to about -50°C.

15. The process as recited in Claim 14, wherein the number of equivalents of the organolithium compound, R^1Li, is 1.5 to about 2.5.

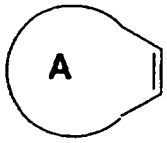
16. The process as recited in Claim 15, wherein the aprotic solvent is tetrahydrofuran.

17. The process as recited in Claim 16, wherein the temperature range is about -78°C to about -70°C.

18. A process for the preparation of a ketone



wherein



represents:

a) 5- or 6-membered heterocyclyl containing one, two or three double bonds, but at least one double bond and 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, the carbocyclyl is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

c) aryl, wherein aryl is as defined below,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

aryl is defined as phenyl or naphthyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$, and when two substituents are located on adjacent carbons they can join to form a 5- or 6-membered ring with one, two or three heteroatoms selected from O, N, and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$,

C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

n is 0 to 5;

R^1 is:

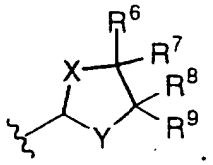
a) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl,

b) aryl, or

c) heteroaryl;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$,

R^2 is OR^4 or $N(R^5)_2$;

R^3 is 

;

R^{3b} is:

a) C_1-C_8 alkyl,

b) aryl, or

c) heteroaryl;

X and Y are independently: O, S, or NR^5;

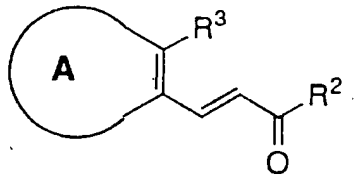
R^4 is C_1-C_8 alkyl;

R^5 is: C_1-C_8 alkyl, or aryl; and

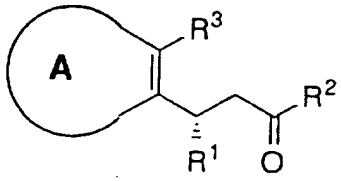
R^6, R^7, R^8 and R^9 are independently: H, C_1-C_8 alkyl, and aryl, such that either R^6 and R^7 are not the same and/or R^8 and R^9 are not the same, or R^6 and R^8 or R^7 and R^9 can join to form a 5- or 6-membered ring, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, or C_3-C_8 cycloalkyl, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R^5)_2$;

comprising the steps of:

1) reacting a α,β-unsaturated ester or amide

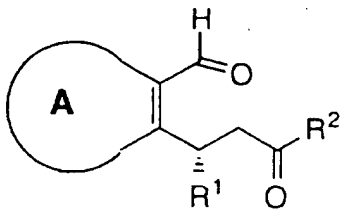


with an organolithium compound, R^1Li, in the presence of an aprotic solvent at a temperature range of about -78°C to about 0°C to give a conjugate adduct



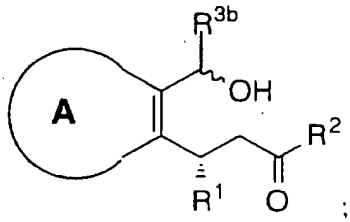
;

2) removing the chiral auxiliary with aqueous acid and tetrahydrofuran to give the aldehyde



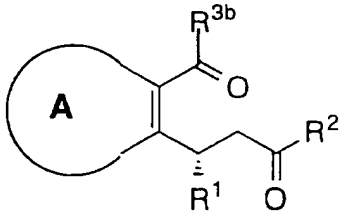
;

3) reacting the aldehyde with a Grignard reagent or organolithium reagent formed with $R^{3b}Z$, where Z is Br, Cl, or I to form an alcohol



;

4) oxidizing the alcohol formed with an oxidizing agent to give the ketone



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19. The process as recited in Claim 18, wherein the number of equivalents of the organolithium compound in the first step is 1 to about 4.

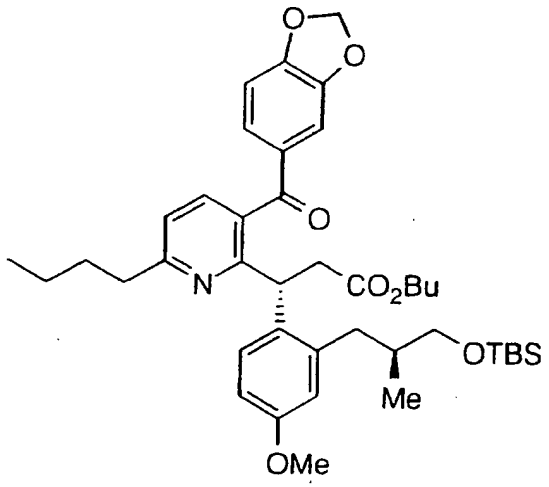
20. The process as recited in Claim 19, wherein the aprotic solvent in the first step is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether, benzene, toluene, pentane, hexane, dioxane and a mixture of said solvents.

21. The process as recited in Claim 20, wherein the temperature range in the first step is about -78°C to about -50°C.

22. The process as recited in Claim 21, wherein the aqueous acid in the second step is aqueous acetic acid.

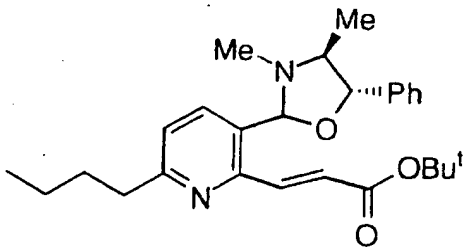
23. The process as recited in Claim 22, wherein the oxidizing agent in the forth step is 4-methylmorpholine-N-oxide and tetrapropylammonium perruthenate(VII).

24. A process for the preparation of a ketone of formula:

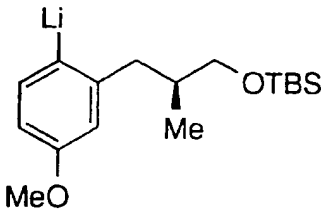


comprising the steps of:

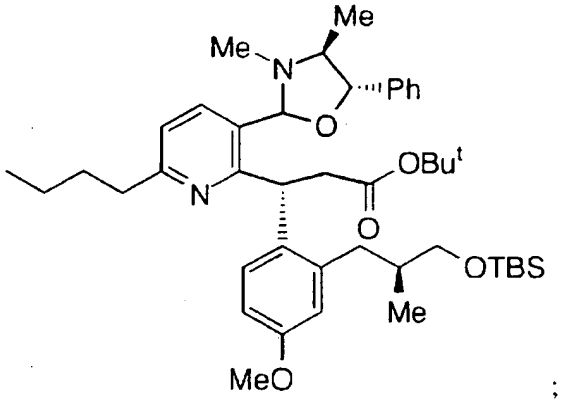
1) reacting a α,β-unsaturated ester or amide



with an organolithium compound

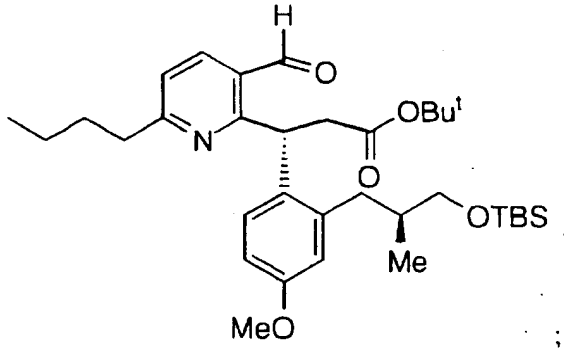


in the presence of an aprotic solvent at a temperature range of about -78°C to about -20°C to give a conjugate adduct



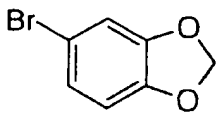
;

2) removing the chiral auxiliary with aqueous acid and tetrahydrofuran to give the aldehyde

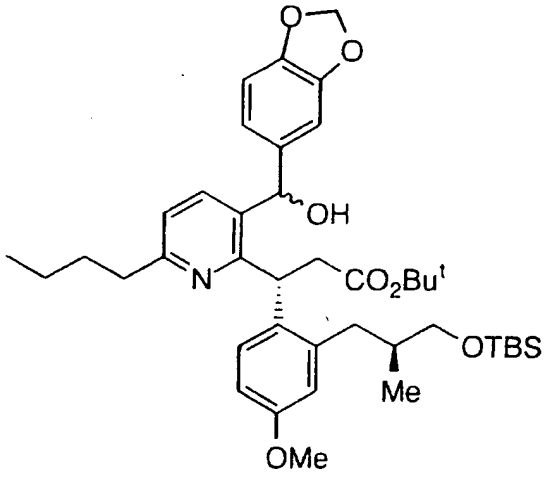


;

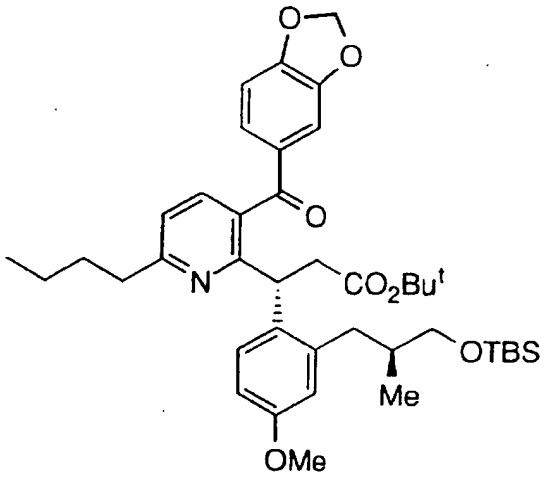
3) reacting the aldehyde with a Grignard reagent or organolithium reagent formed with



to form the alcohol



4) oxidizing the alcohol formed with an oxidizing agent to give a ketone



; and

5) transesterifying the ester with n-butanol and a Lewis acid to give the desired ketone.

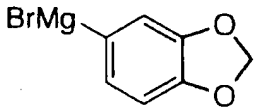
25. The process as recited in Claim 24, wherein the number of equivalents of the organolithium compound in the first step is 1 to about 4.

26. The process as recited in Claim 25, wherein the aprotic solvent in the first step is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl t-butyl ether, benzene, toluene, pentane, hexane, dioxane and a mixture of said solvents.

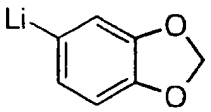
27. The process as recited in Claim 26, wherein the temperature range in the first step is about -78°C to about -50°C.

28. The process as recited in Claim 27, wherein the aqueous acid in the second step is aqueous acetic acid.

29. The process as recited in Claim 28, wherein the Grignard reagent in the third step is



30. The process as recited in Claim 28, wherein the organolithium reagent in the third step is



31. The process as recited in Claim 29, wherein the oxidizing agent in the forth step is 4-methylmorpholine-N-oxide and tetrapropylammonium perruthenate(VII).

32. The process as recited in Claim 31, wherein the fifth step is conducted in the presence of a Lewis acid selected from the group consisting of: $Ti(OEt)_4$, $Ti(OiPr)_4$, and $Ti(OBu)_4$.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/13725

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 213/02, 401/04, 401/06; A61K 31/335, 31/415, 31/42, 31/44

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/338, 340, 341, 355; 546/271.4, 271.7, 273.1, 273.4, 284.4, 315

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966-TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,017,608 A (ASHWANDEN et al.) 21 May 1991, see entire document.	1-32
X --- Y	ALEXAKIS et al. Diastereoselective conjugate addition with acetals, oxazolidines and imidazolines as chiral auxiliaries. Tetrahedron Letters. 1988, Vol. 29, No. 35, pages 4411-4414, especially page 4411.	1-10 --- 1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

24 SEPTEMBER 1997

Date of mailing of the international search report

31 OCT 1997

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/13725

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/338, 340, 341, 355 ; 546/271.4, 271.7, 273.1, 273.4, 284.4, 315